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Published in:
Neuroscience and Biobehavioral Reviews

DOI:
10.1016/j.neubiorev.2020.06.030

Publication date:
2020

Neuroscience and Biobehavioral Reviews 116 (2020) 251–267

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Social withdrawal: An initially adaptive behavior that becomes maladaptive when expressed excessively

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ARTICLE INFO

Keywords:
Sociality
Sociability
Social brain
Evolution
Neuropsychiatric disorders
Etiology
Translational

ABSTRACT

Social withdrawal is found across neuropsychiatric disorders and in numerous animal species under various conditions. It has substantial impact on the quality of life in patients suffering from neuropsychiatric disorders. Often it occurs prodromal to the disease, suggesting that it is either an early biomarker or central to its etiology. Healthy social functioning is supported by the social brain of which the building blocks go back millions of years, showing overlap between humans, rodents and insects. Thus, to elucidate social withdrawal, we have to approach its environmental triggers and its neural and molecular genetic determinants in an evolutionary context. Pathological social withdrawal may originate from a faulty regulation of specific neural circuits. As there is considerable heritability in social disorders, the genetic building blocks of the social decision making network might be our most relevant target to obtain an understanding of the transition of normal social interaction into social withdrawal.

1. Introduction

Disrupted social behavior is a shared symptom of many neuropsychiatric disorders. In particular, withdrawal from social interactions is commonly exhibited in people afflicted with schizophrenia, Alzheimer's disease, depression, and various other neuropsychiatric disorders (American Psychiatric Association, 2013; Porcelli et al., 2019a). There is considerable evidence that the quality and quantity of social interactions in adulthood can have significant effects on an individual's health and well-being: humans and other animals with limited social relationships, or who are socially isolated, have higher rates of mortality and morbidity than those with normal levels of social relations (Cacioppo and Hawkley, 2009; Eisenberger and Cole, 2012; Holt-Lunstad et al., 2010; House et al., 1988). Moreover, the effects of social relationships on mortality even outweigh well-known risk factors such as smoking, alcohol use and high BMI (Holt-Lunstad et al., 2010). Hence, social withdrawal in neuropsychiatric disorders is an important symptom that may cause deleterious effects on disease development, progress and outcome. The precise neural circuit mechanisms underlying withdrawal from social engagement are not well understood, but likely involve structural and/or functional changes within key cortical and subcortical brain structures intimately involved in the regulation of a broad range of social behaviors. This so-called cognitive social brain (Adolphs, 2009; Brothers, 1990; Dunbar, 2009), social behavior network (Newman, 1999) or social decision-making network (SDMN; O'Connell and Hofmann, 2011) has been mapped out in a wide variety of species including humans and has been shown to be evolutionary well-conserved (O'Connell and Hofmann, 2012). This information highlights the significant convergence in the neuroanatomy and neurophysiology of these brain circuits of humans and other animals, as well as in the underlying genetics that shape neural structure and function. Since the phenotype of social withdrawal is not only displayed by mentally-disordered patients but can also be observed in various animal species under different environmental conditions (Dwyer et al., 2015; Fernandez et al., 2017; Henry et al., 2008), animal models can be employed to unravel the neural, molecular and genetic mechanisms of social withdrawal. In literature both social withdrawal and avoidance are used to describe the same phenomenon. Although all social avoidance can be considered as social withdrawal, social withdrawal entails more than only that. In contrast to social avoidance, social withdrawal can also be expressed as a lack of approach or interaction (see for example Hanks et al., 2013; Miyamoto et al., 2017; Seillier et al., 2013; Uribe et al., 2013).

There is a large number of studies that demonstrate that experiences of (social) stress or exposure to sickness-inducing pathogens can lead to retraction of social engagement and interactions (see for example Bluthe´ et al., 1992 & Patel et al., 2018). Yet, a large individual susceptibility exists for these environmental-induced social withdrawal

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https://doi.org/10.1016/j.neubiorev.2020.06.030
Received 12 November 2019; Received in revised form 28 May 2020; Accepted 24 June 2020
Available online 28 June 2020

effects indicating that genetic predispositions appears to play an important role in the development of social withdrawal (see for example Terrillion et al., 2017). These genetic vulnerabilities are often related to neuropsychiatric disorders. This suggests that specific genes are involved in the etiology of both neuropsychiatric disorders as well as social withdrawal behavior. Social withdrawal is, however, also shown to be a highly adaptive response to environmental challenges in a wide variety of species (Dantzer, 2001; Hart, 1988). For that reason, social withdrawal should not by definition be interpreted as a behavioral maladaptive symptom of a disease state, but rather as an adaptive response to the imposed environmental situation that can, when expressed excessively, lead to maladaptive consequences. In this review, we first present social withdrawal as a behavioral symptom of various mental disorders and how it is assessed in humans. Secondly, we highlight social avoidance/approach behavior in rodents and describe its measurement in various different experimental testing paradigms. We then outline the key neural circuitry and its molecular mechanisms underlying social behavior and summarize how the different environmental triggers and biological causes affect these neural mechanisms. With an evolutionary explanation in mind, the review concludes with a discussion of the genetic risk factors for excessive social withdrawal.

2. Social withdrawal as a shared and early symptom of multiple mental disorders

In humans, social withdrawal is often referred to as part of the phenotypic expression of many neuropsychiatric disorders. It can be seen in neurodevelopmental disorders, such as Schizophrenia (Tandon et al., 2009), neurodegenerative diseases, including Alzheimer's disease (Reichman Arnaldo et al., 2001), and other neuropsychiatric disorders, such as Major depressive disorder (Kupferberg et al., 2016). In these disorders social withdrawal is often part of a specific "cluster" of symptoms (e.g. negative symptoms in Schizophrenia or neuropsychiatric symptoms in Alzheimer's disease). Moreover, social withdrawal is the core behavioral symptom of social anxiety disorder (SAD) that is a highly prevalent disorder characterized by persistent fear and avoidance of social interactions (Kessler et al., 1998). Interestingly, in many of these disorders, patients will show signs of negative or neuropsychiatric symptoms (including social withdrawal) even before the disorder-characteristic symptoms arise (see for example Dominguez et al., 2010 & Feldman et al., 2004). Furthermore, the cluster of symptoms that includes social withdrawal is often connected to the worst outcome in terms of functionality and quality of life (see for example Fitzgerald et al., 2001; Rabinowitz et al., 2012; Sousa et al., 2013).

2.1. Schizophrenia and Alzheimer's disease

The symptoms of Schizophrenia (SZ) are often clustered in "positive" or "negative" symptoms. Positive symptoms encompass excessive behaviors not present in healthy individuals, such as hallucinations, delusions and other reality distortions (Tandon et al., 2009). In contrast, negative symptoms are characterized by blunted behavioral functions. Current consensus about the negative symptoms is that they entail blunted affect, poverty of speech, asociality, avolition and anhedonia (Foussias and Remington, 2010; Kirkpatrick et al., 2006). However, these behaviors can be clustered in two distinct categories: 1) Diminished expression, consisting of blunted affect and poverty of speech and 2) Amotivation, consisting of asociality, anhedonia and avolition (Blanchard and Cohen, 2006; Foussias and Remington, 2010; Strauss et al., 2013, 2012). In this second category the symptom of social withdrawal can be found. Patients suffering from Alzheimer's disease (AD) express a symptom cluster similar to the negative symptoms of SZ (Galynker et al., 1995; Reichman et al., 1996; Vercelletto et al., 2002). Here, these symptoms are often referred to as the neuropsychiatric (behavioral) symptoms (NPS) of Alzheimer's disease. Data suggests that NPS are stable during longitudinal assessment (Trigg et al., 2015), although it has also been suggested that specific symptoms (e.g. apathy) can increase as the disease progresses (Conde-Sala et al., 2014). Neuropsychiatric symptoms precede the onset of AD (Feldman et al., 2004). In patients suffering from Alzheimer's disease 88 % also suffers from NPS. Apathy is consistently found to be one of the most occurring neuropsychiatric symptoms. It is reported in about 70 % of AD patients (Khoo et al., 2013), ranging from 44 % to 92 % in patients suffering from mild and severe AD respectively (Mega et al., 1996). Apathy is defined as a loss of motivation, and encompasses behavioral expressions such as social withdrawal, lowered initiative and lack of interest in activities (see for review Landes et al., 2001). As such, apathy appears to show great similarity to avolition as observed in SZ. Indeed, it is argued that they refer to the same phenotype (Foussias and Remington, 2010;Marin, 1991). Also in SZ the negative symptoms are thought to precede other symptoms (Möller, 2007). This is supported by Dominguez et al. (2010) who confirmed that negative symptom expression predicts the onset of positive symptoms (Dominguez et al., 2010). Furthermore, a review by Yung and McGorry (1996) concluded that patients and their family members are reporting negative symptoms (e.g. reduced motivation and social withdrawal) in the (initial) prodromal phase of the disease (Yung and McGorry, 1996). A meta-analysis by Perkins et al. (2005) suggests that patients displaying severe negative symptoms also have a longer duration of untreated psychosis at their first treatment (Perkins et al., 2005). This association is not found with general or positive symptomatology, suggesting a specific role for negative symptoms. A prolonged period of untreated psychosis is linked to a blunted symptomatic recovery and functional outcome for the first psychotic episode (Perkins et al., 2005). As such, earlier detection of negative symptoms, such as social withdrawal, could potentiate treatment by shortening this period.

Negative symptoms themselves have also been associated with poorer functional outcomes. In AD negative symptoms are shown to play a bigger role in the quality of life, when compared to the well-known cognitive deficits (Sousa et al., 2013; Trigg et al., 2015; Zucchella et al., 2015). Rabinowitz (2012) shows that in SZ negative symptoms are a better predictor for functioning than any other symptom type (Rabinowitz et al., 2012). There, negative symptoms have a stronger negative effect on employment (Rosenheck et al., 2006), and are associated with a lowered quality of life (Fitzgerald et al., 2001; Fujimaki et al., 2012). In general, functional outcomes were worse in SZ patients displaying more negative symptoms (Strauss et al., 2013). This was found to be particularly in patients who expressed more behaviors related to the amotivation/avolition category (Foussias et al., 2011; Galderisi et al., 2013; Strauss et al., 2013). Considering its central role in disease outcome, a scientific focus on the 'amotivation/avolition-subtype' and its means of expression, social withdrawal, could provide valuable insight to counter the burden of SZ and AD. Both economically, by increasing productivity, and personally, by increasing quality of life.

2.2. Major depressive disorder and Social anxiety disorder

The implications of social withdrawal are also clear in Major Depressive Disorder (MDD), a disorder that is one of the most profound causes of disability (GBD, 2017 DALYs and HALE Collaborators, 2018; US Burden of Disease Collaborators et al., 2018). When questioned, currently depressed patients report higher levels of social avoidance compared to healthy controls, with remitted patients reporting levels in between the two (Quigley et al., 2017). In MDD, the presence of social withdrawal is linked to anhedonia (Buckner et al., 2008). Anhedonia appears to be the largest predictor of psychosocial functioning in MDD (Vinckier et al., 2017). Young women with high depressive scores expect themselves to respond less positively to social situations, indicating that they expect less pleasure. Furthermore, they engage less in socially rewarding behaviors (Setterfield et al., 2016). Hence it appears as if

social withdrawal in MDD is highly related to motivational deficits, similar to their involvement in SZ and AD. And similarly to those disorders, motivational deficits in MDD show a relationship with both functional impairments and subjective quality of life (Fervaha et al., 2016). Negative appraisal of social company is related to more time being alone; this predicts the onset of depression in females taken from a general population sample (Van Winkel et al., 2017). Furthermore, social rejection (i.e. a passive form of social withdrawal) is a key risk factor for MDD (see for review Slavich et al., 2010). MDD patients seem to process social rejection and acceptance differently than healthy controls (Hsu et al., 2015; Kumar et al., 2017; Stuhrmann et al., 2011). This difference in processing might contribute to the overstatement of negative and understatement of positive experiences seen in MDD. An impairment which is suggested to be involved in the approach/avoidance problems MDD patients suffer from, where approach is thought to be impaired and avoidance to be reinforced (see for review Trew, 2011). Studies trying to objectively show this deficit have difficulties replicating this (Radke et al., 2014; Struijs et al., 2017). MDD patients share an increase in social avoidance with patients suffering from SAD, although the social avoidance levels seen in SAD patients is even higher when compared with those that suffer from MDD only (Ottenbreit et al., 2014). Social anxiety disorder, also known as social phobia, is characterized by discomfort in and avoidance of social situations (see for review Stein and Stein, 2008). Thus, in SAD, social withdrawal is not only part of the disorder, it is the core diagnostic criteria. Interestingly, SAD seems to be contiguous with milder social anxiety (Ruscio, 2010). This suggests that there is no hard cut-off for the display of social withdrawal, but rather that this behavior is widely spread across the general population from which the extremes are seen as symptomatic.

At this moment in time, it is unknown whether the transdiagnostic expression of social withdrawal is originating from a unique neurobiological substrate or whether it involves different proximate mechanisms that reflect different adaptive (or maladaptive) responses. When considering the various psychological constructs underlying social withdrawal it is likely that for each of these underlying constructs, a different biology may arise. For example, a patient with schizoid personality disorder avoids others because of the lack of social reward from the interactions. In contrast, other schizophrenia patients will avoid people as a consequence of their positive psychotic symptoms (e.g., denigrating auditory hallucinations). In addition, social withdrawal in patients with social anxiety disorder is also a defensive strategy but the psychological correlates are different from those of paranoid patients (e.g., fear of being negatively evaluated versus fear of being harmed). Considering these different forms of social withdrawal, this review will focus on the motivational and rewarding aspects of social withdrawal, as well as its underlying neural circuitry.

3. Assessment of human social withdrawal

Although the concept of social withdrawal is recognizable for many, the objective assessment of social withdrawal is challenging. How do you assess if someone exhibits “a loss of social engagement”? In the majority of clinical studies researchers utilize questionnaires, when assessing social functioning and social motivation in the context of neuropsychiatric disorders, such as the social functioning scale (SFS) (Birchwood et al., 1990), Scales for physical and social anhedonia (Chapman et al., 1976), the Snaith–Hamilton Pleasure Scale (Snaith et al., 1995) and the Anticipatory and Consummatory Interpersonal Pleasure Scale (Gooding and Pflum, 2013). Questionnaires have the innate advantage that they are non-invasive and relatively time-efficient. However, questionnaires are also inherently subjective and the individuals answering the questionnaire could be untrustworthy or simply fail to recall details (see for example Kaplan et al., 2008). Though, neuropsychiatric patients seem to be similarly trustworthy as healthy control (Brill et al., 2007). Questionnaires are not the only methods used for the assessment of social behavior/withdrawal. Non-verbal behavior of patients can be studied to assess sociability (see for review Geerts and Brüne, 2009) and certain behavioral tasks have been used to evaluate the social capabilities of individuals (Hynes et al., 2011). Assessments of non-verbal behavior correlate with self-reported information from questionnaires and predict (social) functioning of patients (Brüne et al., 2008; Troisi et al., 2007). These clinical assessments make use of ethograms, a list of behaviors and their descriptions, to score the patients’ behavioral patterns (see for example Grant, 1968; Troisi et al., 1998), similar to how social behavioral is classically assessed in laboratory animals.

3.1. Contemporary methods of assessment

Recently, technological advancements have allowed for new methods to objectively assess social withdrawal in humans. For example, smartphones have allowed studies to assess the “natural habitat” of participants, which is termed “ambulatory assessment” (AA). An often-used simple form of AA is letting subjects respond to queries which are either prompted at set or random times, or self-initiated. This avoids memory constraints often found in questionnaires asking the participants to recall certain events (Trull and Ebner-Priemer, 2013). Taking it one step further is connecting these prompts to occurring events, for example prompting queries when the participant is in a certain geographical location (Törnros et al., 2016). However, recent studies have begun making use of the data collected by the smartphone sensors themselves as proxies for social behavior. Chow et al. (2017) show that social anxiety correlates with time spent at home, a purely geographical measurement (Chow et al., 2017). Furthermore, a study by Dissing et al. (2018) shows that smartphone communication characteristics relate to self-reported social integration and face-to-face contact frequency (Dissing et al., 2018), further demonstrating that data derived from smartphones can be used as a proxy for social behaviors. However, data from smartphones sensors cannot be used to provide proxies of subjective or “perceived’ quality of social relationships that questionnaires or self-reports do include. They can only provide an objective measure of the number/frequency of social contacts and exploratory behavior. There is mounting support for the notion that subjective or perceived quality of social relationships is a stronger predictor of poor health and emotional state in humans than number and frequency of social contacts or social network size (Cacioppo et al., 2010; Hawkley et al., 2006). For example, subjective feelings of loneliness are associated with higher mortality (Perissinotto et al., 2012) and higher rates of hypertension, diabetes, and Alzheimer disease (Hawkley and Cacioppo, 2010; Tomaka et al., 2006; Wilson et al., 2007). This shows that subjective questionnaires can still have an advantage over objective data. More advanced techniques of collecting objective data with smartphones can now provide a detailed view of the social state of an individual. An example of this is the measure of proximity (i.e. distance between the subject and others), which cannot be assessed using questionnaires. Since social withdrawal entails decreased social contact, the distance to peers is most likely reduced considering face-to-face social contact happens in relatively close proximity. With smartphones this distance can be measured, enabling researchers to gain direct insight into the social networks of participants (Boonstra et al., 2017; Eagle et al., 2009). Interestingly, the measurement of proximity does not only relate well to the definition of social withdrawal, it also translates well to the assessment paradigms used in model organisms.

4. Social withdrawal in rodents is classically measured in dyads under artificial conditions

In humans, it is difficult to experimentally manipulate, or assess, the biological mechanisms underlying social withdrawal. Hence, studies have been employed using model organisms to investigate the neurobiological mechanisms underlying social withdrawal. Rodents are

highly social and naturally interact frequently with their conspecifics (Kondrakiewicz et al., 2019). As a matter of fact, in a laboratory setting mice and rats prefer social company over a solitary existence (Balcombe, 2006; Van Loo et al., 2004). They show a preference for places previously associated with social contact (Lott, 1984) and will actively work to obtain social contact (Patterson-Kane et al., 2002; Sherwin, 1996). A multitude of experimental paradigms have been created to assess social approach/avoidance behavior in rodents, from which most are based on the proximity to either a conspecific or a social cue (see for review Peleh et al., 2019). Among the sociability paradigms, one of the best known is the *social interaction test* (SIT). Originally it was developed by File and Hyde (1978) as a behavioral model of anxiety (File and Hyde, 1978). The test is based on the assumption that anxiety and social behavior are negatively associated; that is, rodents that are highly anxious tend to spend less time with engaging with conspecifics. This premise is supported by the fact that anxiolytics increase social interaction (Calabrese, 2008). In this test, 2 non-familiar rodents, of similar weight and sex, are placed in a neutral test arena that permits free exploration between the conspecifics for 5 − 10 min. Typically, the duration of social (approaching, sniffing, allogrooming or following the partner) vs. non-social (rearing, ambulation, autogrooming) behaviors are measured. Although aimed at anxiety, the SIT has extensively been used in research directed at the negative symptoms of schizophrenia, assessing social withdrawal in (pharmacologically induced) models of the disease (Sams-Dodd et al., 1997). In fact, the SIT is one of the key methods to assess face and/or predictive validity of pharmacological models/interventions in SZ (see for example (Rung et al., 2005a,b). However, it can be contested if the social interaction test itself provides adequate face validity to be employed as such. The test only measures a dyadic interaction in a social animal, in which a grouped situation would be ecologically more appropriate (see for example Sutherland et al., 2005). As such, it appears as if the translational and evolutionary relevance of social interactions is disregarded in testing for negative symptoms. However, the social interaction test does provide some interesting results. Injections of NMDAR-antagonists, postulated to act at the core of SZ (Cohen et al., 2015), produce a reduction in social interaction (Rung et al., 2005a,b; Sams-Dodd, 1999), in line with the glutamate hypothesis of SZ. Similarly, a decrease in social interactions has been found in a genetic model of AD using the SIT (Fujiwara et al., 2011). Together, these results indicate that, although the construct validity of the SIT can be contested, the test often exposes the behavioral deviations associated with social withdrawal.

The *social preference/avoidance test* is commonly employed in rats and mice to gauge social preference or social aversion/avoidance behaviors. It operates on the premise that rodents prefer social vs. non-social stimuli. The test can be conducted in a number of different cages and settings, either in a one compartment familiar (home) or neutral cage or in a 3 compartment cage (i.e. the so-called three chamber test (3-CT)) (see for example Brodkin et al., 2004 & Moy et al., 2004). In the one-compartment versions, there are generally two testing sessions. First, the experimental animal is exposed to an empty wire mesh cage and the amount of time investigating the object is recorded. Next, the empty wire mesh cage is replaced with either a novel or familiar conspecific and the amount of time interacting (usually based on distance) is recorded. Generally, most researchers report on the time spent in a so-called interaction zone in the presence of the non-social (empty wire mesh cage) or social target. Increased time spent in the interaction zone in the presence of the social stimulus vs. the non-social stimulus represents social preference. Likewise, less time spent in the interaction zone in the presence of the social target vs. the non-social stimulus represents social avoidance. In the 3-compartment version, the test apparatus consists of three chambers, and an experimental animal is placed in the middle chamber and then has the choice of entering two identical chambers (right and left), one empty chamber and one chamber in which an (unfamiliar) encaged stimulus animal is placed. Spending more time with the stimulus animal is thought to represent sociability (i.e. social preference). See Toth and Neumann (2013) for a review on these behavioral assays and models of social fear and social avoidance (Toth and Neumann, 2013).

Similar to the SIT, the social preference/avoidance tests look only at social approach and avoidance behavior from a dyadic perspective. This is not the desired natural behavior, neither from the rodent perspective nor from a translational perspective, in which the aim is to mimic a human symptom. In these dyadic tests, the animal cannot display its full range of social behaviors. When investigating social withdrawal this is of particular importance because an animal can display social withdrawal either as a lack of motivation to approach and/or interact or as an increased motivation to avoid another conspecific. Additionally, an animal can be avoided by others, which is also seen as a socially withdrawn state. Classical dyadic tests are aimed at assessing only one of these behavioral discrepancies, hence they might miss the others. Furthermore, dyadic tests do not relate to the human situation, as we rarely display our social behavior in a strict dyadic setting.

4.1. Social withdrawal in a semi-natural environment

A way of increasing both ecological and translational relevance is by assessing the full social behavioral repertoire in a group of rodents. Only in these social-housing structures, can social withdrawal from the other members of the social group be truly studied. One of the most well-known systems for the behavioral scrutiny of social group dynamics is the Visible Burrow System (VBS), made famous by the Blanchard group (see for example Arakawa et al., 2007 & Blanchard et al., 1995). The VBS is a semi-natural environment build to resemble a rodent's ecological appropriate environment. It consists of an open-arena and multiple observable nests with tunnels leading to them which together serve as semi-natural burrows. Research using the VBS has been primarily focussed on aggression/hierarchies in rats (see for example Blanchard et al., 2001). However, during the last decade attention has shifted towards the utilisation of mice in this semi-natural environment. This shift has also facilitated the use of transgenic and mutant mouse lines, resembling human neuropsychiatric phenotypes. One of these is the BTBR inbred mouse line. These mice show phenotypic resemblance to the human autism spectrum disorder (ASD) behavioral phenotype (McFarlane et al., 2008). The behavioral deficits of this mouse strain have been investigated in the VBS and subsequently validated using the 3CT by Pobbe et al. (2010). In the VBS BTBR's displayed an impairment in all social behavioral domains, such as approach, aggressive behavior and allogrooming (Pobbe et al., 2010). The decrease in social behavior, observed in the semi-natural environment, could also be replicated in the 3CT. However, whereas the VBS allows for between strain comparison (i.e. BTBR vs control), the 3CT is aimed at providing a 'yes or no' answer concerning social preference within the strain. Due to this, subtle differences between strains might not be picked up. Additionally, due to the longitudinal nature of group-housed approaches, effects of novelty, which might obscure truly social deficits, only play a minor role in the total displayed behavior. This contrasts the classical dyadic test in which (social) novelty is a core part of the test environment.

Groups of mice form a stable hierarchical social structure, consisting of dominant and submissive individuals, typically based on aggressive encounters. Recent studies have shown that the social status within these hierarchies influences gene expression in specific neuronal structures related to social behavior (So et al., 2015; Williamson et al., 2016). This indicates that the social environment of a subject, and its position therein, is important to take into account when studying the mechanism underlying social behavior. A study by Shemesh et al. (2016) shows how investigating the behavior longitudinally in group-housed mice can provide additional information of the effect of genetic manipulation on social behavior, compared to a more conventional approach (Shemesh et al., 2016). Mice deficient for Corticotropin-

releasing factor receptor type-2 in the medial amygdala, a key social structure, show reduced interest in novel mice and increased interest in familiar animals, when tested in a dyadic testing setup. Activation of the neurons targeting the receptor, in wildtype mice, resulted in the opposite, promoting interest in novel and reducing interest in familiar mice. When inhibiting these neurons in a group-housed context social approach was increased. Particularly towards mice of the same social rank, which were approached the least before the neurons were inhibited (Shemesh et al., 2016). In this study all animals of the group were manipulated, however, studies in group-housed mice also provide the unique opportunity to combine treated and untreated animals in one group. Using this semi-natural approach, the biological basis of social withdrawal can now be effectively scrutinized in an ecologically relevant setting that more accurately translates to the human situation.

5. Social approach and avoidance behavior are mainly driven by the brain's social decision-making network (SDMN)

All animals continuously evaluate the saliency of environmental stimuli and respond to it with context-appropriate behavioral actions toward (approach) or away from it (avoidance) (Elliot et al., 2006; Schneirla, 1965). The translation of challenges and opportunities that accompany group living into the spectacular diversity of social behaviors (e.g., investigation, mating, aggression, parenting, affiliation, fleeing) is largely dependent upon distributed processing of social signals across an evolutionary very well conserved social behavior neural network functionally integrated with the basic motivational reward circuitry of limbic forebrain and midbrain areas (see for review Chen and Hong, 2018; Newman, 1999; O'Connell and Hofmann, 2011). The core components of this so-called social decision-making network (SDMN) encompasses the intimately interconnected limbic structures medial and basolateral amygdala (MeA, BLA), bed nucleus of the stria terminalis (BNST), lateral septum (LS), mediodorsal and anterior thalamus (MDT), several hypothalamic nuclei including the anterior hypothalamic (AHA)/medial preoptic (MPOA) area and ventromedial hypothalamus (VMH) as well as the striatal forebrain regions nucleus accumbens/ventral striatum (NAc), hippocampus (HPC) and ventral Pallium (VP). Findings suggest that these limbic areas collectively encompass a hierarchical role in the dynamic encoding of external sociosensory cues and internal physiological signals to cohesively drive adaptive social behaviors that are appropriate to spatial context and dominance status (Chen and Hong, 2018). In addition, important "top-down" modulatory control is provided by various cortical structures (e.g., encompassing Brothers' (1990) and Dunbar's (2009) cognitive social brain) like the orbitofrontal (OFC), medial prefrontal (mPFC), insular (IC) and anterior cingulate cortex (ACC), as well as the ascending midbrain monoaminergic nuclei like the dorsal/medial raphe nucleus (DRN/MRN; serotonin), locus coeruleus (LC; noradrenaline) and ventral tegmental area (VTA; dopamine). The production of the autonomic and somatic motor output aspects of the various social behavioral elements are to a large extent coordinated by the periaqueductal gray area (PAG) (see O'Connell and Hofmann, 2011; Prounis and Ophir, 2020; Rogers-Carter and Christianson, 2019 for more detailed reviews of the various cortical and non-cortical neural structures that comprise the social brain network). Extensive comparative research demonstrated that this highly interconnected neural network for social behavioral functioning is remarkably similar in many vertebrate species including human beings, indicating that it is evolutionary ancient and phylogenetically conserved (Goodson, 2005; O'Connell and Hofmann, 2012). Indeed, this basic SDMN circuitry (at region level) is generally confirmed in humans by modern brain-imaging techniques that allow the in-vivo functional/structural (fMRI) analysis of the neuronal nodes/networks and of its associated neurochemistry (PET/SPECT) that are involved in social behaviors (see for reviews (Bickart et al., 2014; Porcelli et al., 2019a; Rogers-Carter and Christianson, 2019). Obviously, the functional activity of this social behavior neural decision-making network, and thereby the selection of the appropriate behavioral response to social challenges and opportunities, is determined by a wide variety of molecular substrates (i.e., neurotransmitters, hormones, cytokines, and their respective metabolic enzymes, receptors, and intraneuronal signaling molecules). Undisputedly, among the neurochemical systems that are considered key signaling molecules in this neurocircuitry controlling social behaviors are the main inhibitory/excitatory amino acids (GABA/Glutamate), canonical monoamines serotonin (5-HT), noradrenaline (NA) and dopamine (DA), the "social" nonapeptides oxytocin (OXT), and vasopressin (AVP), the "hedonic" endogenous opioid peptides, the "stress" HPA- and "sex" HPG-axis's neuropeptides (corticotropin releasing factor (CRF)) and steroid hormones (corticosterone, testosterone, estrogen), and their cognate receptors. Indeed, the neurons in the SDMN regions as outlined above, abundantly receive these neurotransmitter projections and express a variety of their membrane-bound receptors, including serotoninergic 1A/B, 2A/C, dopaminergic DRD1/2 and vasopressin/oxytocin AVP1A/B/OTR receptors, the mu, delta and kappa opioid receptors as well as the intracellular steroid hormone androgen (AR), estrogen (EsR1/2), progesterone (PR), mineralocorticoid (MR) and glucocorticoid (GR) receptors. Since levels of many of these neuromodulators change rapidly and dynamically before, during and after the execution of different social behaviors, they may influence the various nodal neuron excitabilities and hence the initiation, maintenance and termination of different social behaviors as well as the consequent processing of social experiences.

6. Neuropsychiatric disorders correlate with malfunctions in the social decision-making network

Compared to healthy controls, neuronal anomalies have been discovered in patients suffering from multiple neuropsychiatric disorders (see for review Porcelli et al., 2019b). In SZ, cortical grey matter is reduced in the frontal regions before the onset of the disorder (Cannon et al., 2015). After disease onset, SZ patients show brain volume differences in a wide variety of areas, when compared to healthy controls. The hippocampus, amygdala, thalamus and NAc were all smaller in SZ patients, and larger lateral ventricle volumes were also observed (Van Erp et al., 2016). In AD, structural changes related to the neuropsychiatric symptoms, apathy in particular, were mainly found in the OFC and ACC. However, more areas appear to be involved, such as the amygdala and the VTA (Boublay et al., 2016; Theleritis et al., 2014). Other neuronal abnormalities have also been associated with AD, including volumetric reductions and/or neurotransmitter deficits. Some related to components of the SDMN (see for review Hardy et al., 1985). Cell loss is found in the LC, the main site of NA production, and lowered concentrations of NA and loss of NA innervation are seen in multiple areas including the hypothalamus and cingulate cortex (Hardy et al., 1985). Considering MDD, many areas related to the SDMN connect the disorder to social withdrawal. After social rejection MDD patients show increased activation in their amygdala, insula and ventrolateral prefrontal cortex (Kumar et al., 2017), which are all part of social brain networks (Bickart et al., 2014). Depressed patients also show deactivation of opioid receptors in the amygdala and blunted activation in the NAc, thalamus and periaqueductal grey during rejection. Similarly, during social acceptance (de)activation patterns differed from healthy controls, where activation of the amygdala was only seen in controls and deactivation of the NAc was only seen in patients (Hsu et al., 2015). Additionally, responses of particular neuronal structures to either positive facial expressions (e.g. happy) or negative facial expressions (e.g. sad) differed between MDD patients and healthy controls. In reaction to positive stimuli a decreased response could be seen in the amygdala, insula and striatum. Whereas negative stimuli led to hyper-responsiveness in the amygdala, insula and striatum, a decrease in OFC activation could also be observed (Stuhrmann et al., 2011). Thus, abnormalities in the activation of components of the SDMN in response to

both positive and negative social stimuli can be observed in MDD, where the response to positive stimuli is blunted and the response to negative stimuli is exaggerated. This skewed response to opposite salient emotional cues may indicate a dysfunctional OXT system which is supported by the finding of reduced plasma OXT levels in depressed patients (Jobst et al., 2015). In SZ, a long-standing hypothesis suggests that dopamine is a key factor, which has been supported by elevated DA synthesis capacity, release and baseline synaptic levels in patients. Presynaptic dysregulation appears to be at the core of this (for review see (Howes and Murray, 2014)). In AD, dopamine dysfunction can be found at any point during the progression of AD, which is possibly related to the expression of apathy (Martorana and Koch, 2014). Another line of reasoning suggests a great importance of glutamate and GABA in SZ, which is similarly based on years of evidence (see for review (Cohen et al., 2015)). The origin can be found in the observation that phencyclidine (PCP) leads to a SZ-like phenotype in healthy individuals (Luby et al., 1959). This suggested a central role for the NDMA-receptor, for which PCP is an antagonist. Indeed, NDMA-receptor expression levels are reduced in post-mortem PFC samples of SZ patients (Weickert et al., 2013). This subsequently may relate to reduced GABA-ergic activity, as antagonism of the NMDA-receptor to a decrease in activity of prefrontal GABA-ergic interneurons. Interestingly, treatment with a NMDA-receptor antagonist also has a, delayed, excitatory effect on pyramidal neurons, which are thought to play a critical role in executive functions (Homayoun and Moghaddam, 2007). In rats, a bilateral infusion of a GABAA-receptor antagonist into the medial prefrontal cortex or basolateral amygdala leads to social withdrawal (Paine et al., 2017). Patients suffering from SZ appear to have lowered cortical GABA-functionality when compared to healthy controls (Lewis, 2014). This lowered functionality appears to be already visible during the prodromal stage of the disease, as is apparent by lowered cortical gamma oscillatory power (Minzenberg et al., 2010). In AD, a wide variety of neurotransmitter systems contribute to the neuropsychiatric symptoms, as the cholinergic, noradrenergic, serotonergic and dopaminergic systems all seem to play a role (Boublay et al., 2016). Waldemar et al. (2011), shows that donepezil, a cholinesterase inhibitor, prevents/decelerates the formation of apathy in AD (Waldemar et al., 2011), indicating a role for the cholinergic system specifically in this symptom. Furthermore, cell loss in the raphe nucleus and a reduction in both 5-HT itself and its receptors has been reported (Hardy et al., 1985). The treatment of MDD has primarily focussed on the 5-HT, making use of *selective serotonin reuptake inhibitors* (SSRIs) which primarily target the serotonin transporter (SERT). Indeed, the serotonergic system seems to be affected in MDD. Patients show lower blood levels of 5-HT and its precursor, and the SSRIs used for the treatment of MDD lead to increased extracellular 5-HT availability. Furthermore, there seems to be an involvement of all 5-HT receptors in MDD (see for review Fakhoury, 2016). Specifically, reduced SERT-receptor binding in the striatum and amygdala was found in depressed patients (Kambeitz and Howes, 2015) and reductions in 5-HT_{1a}-receptor binding was found across a wide variety of brain areas, including the amygdala, ACC and the raphe nucleus (Drevets et al., 1999; Wang et al., 2016).

7. Social behavior and the reward system

From the above, it is clear that neuropsychiatric disorders correlate with changes in both the structural components of the SDMN and related neurochemical function properties. This includes parts of the SDMN mainly dedicated to motivation and reward. When discussing social withdrawal, a behavior related to approach and avoidance, a connection to the hedonic reward systems seems like a natural step. Indeed, Kirschner et al. (2016) propose a discrepancy in adaptive coding of rewards in SZ patients as a key part in negative symptoms (Kirschner et al., 2016). Foussias and Remington (2010) argue that primarily the anticipation of pleasure is affected in SZ rather than the consumption (Foussias and Remington, 2010). Studies confirm this suggestion (Gard et al., 2007; Mote et al., 2014), although discrepancies can be found in the literature, including studies that have used similar methods (Chan et al., 2010; Strauss et al., 2011). Deficits in anticipatory pleasure correlate with negative symptoms (Chan et al., 2010; Mote et al., 2014) and are also observed in patients with recent onset diagnosis (Mote et al., 2014), preceding the positive symptoms. Chan et al. (2010) confirm the relationship between anticipatory pleasure and social withdrawal in Chinese SZ patients, however they also show a relation with consummatory pleasure (Chan et al., 2010). Edwards et al. (2015) suggest a greater discrepancy between anticipated and consummatory subjective valence in SZ patients, as a possible explanation (Edwards et al., 2015). Taking this into consideration, it appears as if SZ patients suffer from a deficit in judging rewards.

Studies using non-human animals have previously shown that social behavior in itself can be rewarding (see for review Trezza et al., 2011). In humans, social rewards and monetary rewards show overlap in their neuronal activation pattern (Izuma et al., 2008; Lin et al., 2012). One exception was the amygdala, which was only activated during the consumption of a social reward (Rademacher et al., 2010). In rodents it has been shown that social interactions can be highly rewarding and indeed recruit components of the brain's reward circuitry (Dölen et al., 2013; Robinson et al., 2002). Thus, a deficit in components of the reward system could lead to the disruption of social rewards, ultimately leading to social withdrawal (for review see (Krach et al., 2010)). Hung et al. (2017) show necessity for social reward processing of dopaminergic neurons in the VTA driven by OXT. Social interaction activates oxytocinergic neurons in the paraventricular nucleus (PVN) that project to the VTA. Mice lacking OXT-receptors in the targeted dopaminergic neurons in the VTA or mice from which the PVN originating oxytocinergic neurons were inhibited displayed a reduction specifically in the processing of social rewards (Hung et al., 2017). Interestingly, OXT also rescues the display of social withdrawal after treatment with PCP (Kohli et al., 2019). Borland et al. (2018) show evidence that OXT injected into the VTA decreases (experienced) social reward value, while an OXT-receptor antagonist increases it (Borland et al., 2018). The aforementioned dopaminergic neurons of the VTA project to GABAergic medium spiny neurons in the NAc and olfactory tubercle of the ventral striatum (Haber and McFarland, 1999), making it part of the SDMN. Interestingly, the avolition subtype of SZ relates to hypoactivation in the ventral part of the striatum (i.e. NAc) during reward anticipation (Kirschner et al., 2015). Moreover, MDD is related to hypoactivation of this same area (Kupferberg et al., 2016). When an animal is exposed to a reward, the dopaminergic reaction to this reward adapts based on the predicted value of the reward (Tobler et al., 2005). This allows the reward system to discriminate between the almost endless possibilities of rewards. Interestingly the striatum, and its connectivity to other reward structures, appears to be key in the adaption to rewards (Park et al., 2012).

7.1. Opioid receptors and social rewards

Another important neurochemical system that is implicated in the modulation of social reward are endogenous opioid and the mu-opioid receptors. The μ-opioid receptor (MOR) system has also been shown to interact with oxytocin and dopamine in social bonding and social reward (Smith et al., 2018). Originally formulated by Panksepp, the brain opioid theory of social attachment posits that opioids contribute to emotional responding within close relationships and to the behavior or feelings that might promote further bonding (Inagaki, 2018; MacHin and Dunbar, 2011; Panksepp et al., 1980). Hence, reductions in opioid activity should increase desire for social companionship, and increases in this system should reduce the need for affiliation. Extensive data from animals (for reviews, see Inagaki, 2018; Loseth et al., 2014) suggest that opioids are released during affiliative behavior and increase feelings of social connection, whereas inhibiting opioids (resulting in low opioid tone) motivates social contact and increases feelings of

social disconnection. Pharmacologically altering opioid activity with opiate drugs leads to similar effects on social behavior and feelings of social connection. For example, animals treated with moderate doses of opiates tend to socially isolate themselves; conversely, the opioid antagonists naloxone and naltrexone have opposite effects, increasing affiliation. In addition, genetic mutations of the mu opiate receptor (MOPR) that alter receptor function can influence social behavior in a variety of animal models and humans (Barr et al., 2008; Moles et al., 2004; Pearce et al., 2017). The nonsynonymous single nucleotide polymorphism (SNP) A118 G within the MOPR gene (OPRM1) is commonly seen in European (15–30 %) and Asian (49–60 %) populations (Bergen et al., 1997; Gelernter et al., 1999; Tan et al., 2003). Individuals that carry the G-allele have an increased tendency to become engaged in affectionate relationships and experience more pleasure in social situations (Troisi et al., 2011).

8. Rodent models of social withdrawal target the social decision-making network

The fact that various neuropsychiatric disorders that present social withdrawal symptoms are precipitated by different environmental triggers (such as exposure to adverse stressors or infectious agents) or certain biological causes (neural manipulations, pharmacological agents, genetic mutations) is well documented. Therefore, many animal models of social withdrawal are based on the application of stressors, or infectious/pharmacological agents either during their developmental period or during adulthood. In addition, some models recapitulate other possible etiologies of social withdrawal by directly targeting the putative underlying biological substrate like alterations in specific brain circuitries or distinct genes that are believed to be associated with social withdrawal/avoidance. Following are several examples of these employed strategies

8.1. Direct manipulations of the SDMN

Functional magnetic resonance imaging, electrical, pharmacological and optogenetic stimulation and lesion studies have begun to delineate the key neurons and neural circuits within the SDMN that specifically subserve social approach/avoidance behaviors. Notably, the mPFC has emerged as a crucial “top-down” neural substrate for controlling social interaction in both humans (Bicks et al., 2015; Dolan, 2002) and other animals (Kim et al., 2015; Yizhar, 2012). Major structural and functional changes in the PFC have been documented in human imaging and postmortem studies of patients with MDD, autism and schizophrenia (Amaral et al., 2008; Drevets et al., 2008; Tan et al., 2007). These changes generally include reduced neuronal PFC activity of MDD patients (Drevets et al., 2008), but increased PFC activity (increased excitation and inhibition (E/I) balance) in autism and schizophrenia (Lewis et al., 2005; Rubenstein and Merzenich, 2003). Neural activity in the mPFC correlates with social approach behavior in mice (Lee et al., 2016). A subset of mPFC neurons exhibited elevated discharge rates while mice approached the social target in a three-chamber sociality test (Kim et al., 2015). Accordingly, selective pharmacogenetic inhibition of glutaminergic mPFC neuron projections to specifically the PAG increased social avoidance (Franklin et al., 2017). In contrast however, acute optogenetic excitation of mPFC projections to dorsal raphe nucleus or lateral habenula has been reported to impair social functioning and to induce social avoidance (Benekareddy et al., 2018; Challis et al., 2014; Yizhar et al., 2011). Accordingly, NMDA receptor dysfunction in the mPFC increases social approach behavior in mice (Finlay et al., 2015). Hence, similar to human findings indicated above, both hypo-activity and hyper-activity of mPFC seems to be able to decrease sociability in rats and mice, likely depending on the specific cluster of mPFC neurons involved or experimental paradigm used.

A major projection target of the PFC, and important SDMN structure regulating social approach and avoidance, is the amygdala. The amygdala may mediate social facilitation, in part, via projections to the ventral hippocampus. A recent study optogenetically manipulated the projections from pyramidal neurons in the basolateral amygdala to the ventral hippocampus in mice performing social interaction tests. Deactivation of these projections significantly increased social interactions, whereas activation of the projections decreased social interactions (Felix-Ortiz and Tye, 2014).

Another often employed pharmacological method to induce social withdrawal in rodents is sub-chronic treatment with PCP, an antagonist of the NMDA-receptor (see for example Seillier and Giuffrida, 2009). Utilizing this model, Matricon et al. (2016) have studied which activity pattern the brain expresses during the display of social withdrawal (Matricon et al., 2016). Firstly, they show that after exposure to the SIT, other brain areas were more activated, measured by means of c-fos expression, than after a non-social exploratory task. Contrasting activation patterns were found in the brain areas connected the SDMN, as deviations in expression can be found in the infralimbic cortex (IL), OFC, dorsomedial caudate putamen (dmCPu), ventrolateral septum (VLS), posterior nucleus of the central amygdala (pCeA) and dorsolateral PAG. Interestingly, many of these changes were blocked by inducing social withdrawal through PCP-treatment. PCP-treatment prevented the changes in c-fos activation in the IL, OFC, dmCPu, VLS and pCeA. Furthermore, PCP-treated animals showed activation of the dorsomedial BNST after exposure to the SIT and a decrease in c-fos positive cells in the basolateral amygdala and VTA after both the social and non-social task (Matricon et al., 2016). Effects of PCP on the VTA were shown to be reproducible as they were also found by another study (Katayama et al., 2013). Interestingly, many of the areas affected by PCP-treatment appear to play a key role in the mesolimbic reward system and overlap with the SDMN. However, the social effects of PCP might be non-specific, as PCP is known to have general rewarding actions (Carlezon and Wise, 1996). Effects of pharmacological interventions on social withdrawal are not confined to the glutamatergic pathway; other neurotransmitter systems related to the SDMN are also involved (see for review Gururajan et al., 2010). Pharmacologically targeting the Dopaminergic system by injections of amphetamine in rats has provided conflicting results regarding social withdrawal. After acute treatment, both increases and decreases in social behavioral levels have been found. However, after chronic treatment evidence seems to favor a social withdrawal inducing effect (Gururajan et al., 2010). Other pharmaceuticals affecting the dopaminergic system have also been tested on their effects on social withdrawal. Classical antipsychotics, such as haloperidol and chlorpromazine, tend to induce social withdrawal in the SIT. Whereas atypical antipsychotics lead to an increase of social behavior (Corbett et al., 1993). Concerning the serotonergic system, acutely 3,4-methylenedioxymethamphetamine (MDMA) seems to have prosocial effects, both in humans and rodents (see for review (Kamilar-Britt and Bedi, 2017)). MDMA initially leads to an increase in the extracellular availability of 5-HT (Nichols et al., 1982), coinciding with its acute effects. However, the long-term pretreated rodents show lowered 5-HT availability in the hippocampus, frontal cortex, striatum and amygdala, coinciding with a display of social withdrawal (Bull et al., 2004; McGregor et al., 2003). Indeed, sub-chronic treatment with MDMA has consistently been found to lead to social withdrawal (Gururajan et al., 2010). Taken together, it is clear that pharmacological interventions targeting the neurotransmitters central to the SDMN can have profound effects on social withdrawal.

8.2. Effects of infection

However, this same network can also be targeted by making use of more naturally occurring biological triggers, namely exposure to pathogens or stressors. Injecting rodents with lipopolysaccharide (LPS), the part of gram-negative bacteria that is recognized by the immune system as a pathogen (Wang and Quinn, 2010), causes a strong reduction in social exploration (Bluthe et al., 1992), as part of the sickness

syndrome. Furthermore, in rats that were intraperitoneally (i.p.) injected with LPS, impairments in social behavior could be partly attenuated by an i.p., but not intracerebroventricular, injection of an interleukin-1 (IL-1) receptor antagonist (Bluthe et al., 1992). This suggests a role for peripheral cytokine IL-1 in social behavior. However, other cytokines such as interleukin-6 (IL-6) also seem to play a role (Bluthé et al., 2000). Interestingly, these cytokines also seem to affect the SDMN. After injecting rats with IL-1, c-fos activation can be found in several areas including the amygdala and catecholaminergic neurons of the nucleus of the solitary tract (NTS) (Brady et al., 1994), which project to the amygdala (Zardetto-Smith and Gray, 1990). Immediate-early gene expression in the amygdala is also found after i.p. administration of IL-6 in mice (Tinsley et al., 2001). Moreover, multiple cytokines seem to modulate neurotransmitters such as dopamine (DA), norepinephrine (NE) and serotonin (5-HT) in either the amygdala or another part of the SDMN such as the striatum (see for review Dunn, 2006).

8.3. Effects of stress

Similar to pathogens, stress also can induce decreased social behavior (see for example Colyn et al., 2019) and it is known to also enhance plasma cytokine levels (Cheng et al., 2015). Stress can be highly heterogenic in nature, it can be experienced acutely or chronically and it may be of social or non-social origin. A wide variety of stressors seem to induce decreases in social interaction or increased social avoidance in rodents (see for review Toth and Neumann, 2013). However, social and non-social stressors seem to have differential behavioral effects. When focusing on chronic stressors, chronic mild stress (CMS) does not seem to lead to social withdrawal (Venzala et al., 2013) or only under certain conditions (Gross and Pinhasov, 2016). An often-used non-social stressor is chronic restraint stress (CRS), but the effects of this stressor also vary. Studies using adult rats have shown both increased social approach behavior (Li et al., 2016) and social withdrawal (i.e. decreased interaction and increased avoidance) (Varlinskaya et al., 2018; Zain et al., 2019) after CRS, although differences might be based on methodological discrepancies. Chronic social stress, in the form of chronic social defeat stress (CSDS), appears to lead to more stable effects on social behavior, as it frequently has been shown to induce social avoidance in vulnerable animals (see for example Bondar et al., 2018; Colyn et al., 2019; Ito et al., 2017; Patel et al., 2018). This has led to the use social avoidance as a behavioral biomarker for social defeat stress (SDS) allowing the selection of susceptible and resilient individuals. In non-manipulated individuals, vulnerability to SDS relates to multiple factors, including trait anxiety and increased cytokine (IL-6) levels (Nasca et al., 2019). Interestingly, stress induced behavioral changes also coincide with changes in the SDMN brain nodes. Structural changes can be seen in the PFC, hippocampus and BLA. After CSDS dendritic connectivity is found to be downregulated in the PFC and hippocampus and upregulated in the amygdala (Colyn et al., 2019; Patel et al., 2018). Also neurotransmitter systems are affected by CSDS. Francis et al. (2015) show that activity concerning two subtypes of medium spiny neurons in the NAc, one enriched with the dopamine receptor D1 and the other with D2, is influenced by CSDS. Whereas excitatory input is increased in the D1 subtype, it is decreased in the D2 subtype of the medium spiny neurons. Furthermore, modulating the activity of these neurons can influence the effects of CSDS, as activating the D1 neurons results in resilience against the stressor and inhibition induces the behavioral outcomes (Francis et al., 2015). Besides dopamine, the oxytocinergic system also appears to play a role, as OXT infusion can rescue the social deficits caused by CSDS (Lukas et al., 2011). Interestingly, the effects of CSDS on social avoidance in susceptible animals can also be blocked by countering (neuro)inflammation (Ito et al., 2017). This demonstrates the potential overlap between pathways involving pathogen or stress exposure leading to changes in SDMN, ultimately leading to social withdrawal.

8.4. Genetic manipulation

Social behavioral deficits can also be induced by manipulating the genetic building blocks of the pathways the aforementioned induction methods act on. Mice deficient for GluN3A, a gene coding for a subunit of the NMDA-receptor, show clear hallmarks of social withdrawal, including social avoidance and reduced social interaction, which could be rescued by oxytocin (Lee et al., 2018). Knocking-out the oxytocin receptor itself similarly leads to a similar phenotype in which social interactions are reduced and avoided, both in the VBS and in classical behavioral tests (Pobbe et al., 2012). Regarding the pathway via which the immune system influences social behavior, genetic manipulation of toll-like receptor-2 (TLR-2) has also been shown to lead to social discrepancies. Mice in which the TLR-2 is knocked-out show a clear reduction in social interaction time, although they did not display social avoidance (Park et al., 2015).

9. Social behavior is highly conserved

It is clear that social affiliative behavior is not unique to humans. Animals from various taxa show a certain degree of sociality (i.e. group-living) and even outside the animal kingdom social behavior can be observed. Amoeba (Gregor et al., 2010), roundworms (McBride and Hollis, 1966), the common fruit fly (Ramdya et al., 2017; Soto-Yéber et al., 2018), mice (Kondrakiewicz et al., 2019) and primates (Kudo and Dunbar, 2001), all tend to be social in one way or another. Such a wide range of species showing comparable behaviors hints towards conserved biological mechanisms that control these behaviors. This is confirmed in the finding that the part of the body that principally controls human social behavior, the social brain, goes far back on the evolutionary tree. O'Connell and Hofmann (2012) show that the SDMN has been conserved over 450 million years of evolution, the time of the last common ancestor of the ray-finned fish and tetrapods (O'Connell and Hofmann, 2012). Arendt et al. (2016) propose that the evolution of the brain dates back to a common ancestor of the cnidarians (i.a. jellyfish) and bilaterians (i.a. insects and vertebrates) (Arendt et al., 2016). The building blocks of the system controlling social behavior may thus stem from a common ancestor for many of our typical model organisms including *caenorhabditis elegans*, *drosophila melanogaster*, *mus musculus* and *rattus norvegicus*. This would suggest that similar mechanisms can be found that drive social behavior, which could be expected to respond alike to similar (changes in) neuroactive agents. Interestingly, dopamine seems to have modulatory effects on social behavior across taxa. In *c. elegans* dopamine administration leads to an increase in social behavior, whereas antipsychotics and antagonists for the Dopamine D2 receptor (DRD2) decrease aggregation (Dwyer et al., 2015). Fernandez et al. (2017) show that manipulation of the dopaminergic system, leading to a reduction of Dopamine availability, decreases sociability in *drosophila m.* (Fernandez et al., 2017). In mice, lowered social interaction time can be found when atypical antipsychotics are administered (Corbett et al., 1993). These antipsychotics all show antagonism for at least one of the dopaminergic receptors. Not only manipulation of the dopamine system can alter social behavior in distant species, substances affecting serotine pathways show similar evolutionary conservatism. As stated before, MDMA has prosocial effects, in humans and rodents (see for review (Kamilar-Britt and Bedi, 2017). However, similar effects can be found in cephalopods, as MDMA infusion led to increased social interaction in *octopus bimaculoides* (Edsinger and Dölen, 2018). This suggest that the biological basis of social behavior is highly conserved and present in virtually all species. Social behavior is a way for organisms to cope with living in a group and is thus a necessity for most species (Alexander, 1974). Intuitively this would exclude solitary species. However, solitary species also show signs of sociality. Elbroch et al. (2017) provide evidence that the cougar (*puma concolor*), a large "solitary" carnivorous felid, displays social strategies similar to that of more social animals. All assessed cougars

were part of a social network in which they displayed a hierarchy. At large carcasses conspecifics tolerated each other, which was explained by direct reciprocity. Interestingly, this tolerance was not explained by kinship (Elbroch et al., 2017). More studies are reporting sociality in classically "solitary" species (see for example Wagner et al., 2008 & Wiens and Zitzmann, 2003) indicating that social behavior is widespread across animals.

10. Short-term social withdrawal is adaptive

10.1. An adaptive response to social stress

Although evolution has shaped social structures for optimal survival by favoring cooperative exchanges, social interactions are often the main source of stress that may negatively impact the health and well-being of certain (susceptible) individuals (Koolhaas et al., 2011). Social stressors ranging from acute social conflicts and defeat to chronic social instability and sustained social subordination recruit a highly conserved biological machinery principally positioned to effectively deal or cope with these adverse social life situations.

Social hierarchies are a way for group-living organisms to organize themselves in order to assure the allocation of limited resources such as food or mates. Although these hierarchical structures entails both winners and losers, most species seem to have the tendency to organize into social hierarchies, including groups of humans (see for review Koski et al., 2015). While it is currently under discussion how stress is related to rank, it is clear that whenever there is a dispute over the hierarchical status quo this leads to a social conflict (Sapolsky, 2005). In such a dispute, the losing animal (i.e. the subordinate) experiences a situation that closely resembles that of social defeat as described above. Subordinate mice display decreased social interactions when compared to dominant mice in the same colony (So et al., 2015). This suggests a socially withdrawn phenotype, comparable with that seen after CSDS. Indeed, subordination in a colony has been put forward as a model for chronic social stress (Blanchard et al., 1995). This chronic stress might be leading to the observed social withdrawal phenotype, leading to avoidance of the stressor (i.e. the dominant animals). Avoidance of adverse and stressful situations can be considered an effective adaptive response, as further harm is avoided. Usually dominant animals cease their overt aggressive acts and attacks towards other animals that clearly signals social subjugation and submissiveness. This suggest that, in healthy animals, the cue of a submissive display (incl. withdrawal) prevents the continuation of aggression and thus further harm (Natarajan et al., 2009; Tinbergen, 1952).

10.2. An adaptive response to infection

Group size and contagious parasitism show a positive correlation (Cote and Poulinb, 1995; Patterson and Ruckstuhl, 2013; Rifkin et al., 2012). Thus, certain (social) behavioral changes should have evolved to adapt to the increased susceptibility to pathogens in groups. The most obvious behavioral adaptation that could relate to this is "sickness behavior". Sickness behavior refers to an all-out adaptive response to pathogens, which was first described, as such, by Benjamin L. Hart (Hart, 1988, 1985). It is characterized by a variety of behavioral changes, including anorexia, lethargy, depression and reduced grooming, and is thought to be mainly induced by cytokines such as IL-1 (Hart, 1988). Further research into sickness behavior confirmed that cytokines indeed lead to the symptoms mentioned above, including anhedonia and social withdrawal (see for review Dantzer, 2001 & Larson and Dunn, 2001). The behavioral display shown after infection is thought to conserve energy to efficiently counter the pathogen (Hart, 1988). Supporting this is the fact that although animals show social withdrawal (e.g. as increased social avoidance/decreased approach) they increase their huddling behavior (Yee and Prendergast, 2010), which is a key component in thermoregulation and thus energy expenditure.

The display of sickness behavior after infection can be mimicked by injecting rodents with the injection of lipopolysaccharide (LPS), which also leads to social withdrawal (Bluthe´ et al., 1992). However, exposing a rodent to LPS does not only modulate the behavior of the "infected" individual, it also effects its conspecifics. Boillat et al. (2015) showed that rodents prefer non-infected individuals (Arakawa et al., 2010; Boillat et al., 2015), however this behavior might depend on previous experiences (Renault et al., 2008). Similar to sickness behavior, avoidance of infected individuals can be seen in multiple species. Healthy Caribbean spiny lobsters (*panulirus argus*) tend to avoid individuals that are infected (Behringer et al., 2006). Also humans appear to show tendencies of social avoidance when questioned about their willingness to interact with a person suffering from a variety of illnesses (Crandall and Moriarty, 1995). As such, pathogens appear to modulate both the activity of the host as well the activity of its conspecifics leading to social withdrawal both by and from the infected animal. In humans, withdrawal from the infected individual appears to rely, at least partly, on facial cues, as Axelsson et al. (2018) show that subjects are able to recognize LPS injected individuals based only on facial cues from pictures taken 2 h after the injection (Axelsson et al., 2018). In rodents, odor appears to play a key role. Rats tend to show more avoidance and less sniffing of soiled bedding derived from LPS/interleukin-1 injected conspecifics, compared to that derived from conspecifics injected with saline (Arakawa et al., 2010). Boillat et al. (2015) show that the preference for healthy versus infected conspecifics can be mitigated by removing part of the olfactory system (i.e. the vomeronasal organ) in mice. The use of the olfactory system in sickness recognition is, however, not unique to rodents. This method has also been found in primates. Mandrills (*mandrillus sphinx*) show a similar avoidance of faecal samples of infected individuals (Poirotte et al., 2017), supporting the hypothesis that odour plays a crucial role in the recognition of sick conspecifics. As such, it is clear that both the infected animals as its peers show an adaptive form of acute social withdrawal in response to pathogen exposure. Either to conserve energy and counter the pathogen or to attempt to avoid the pathogen.

11. Long-term social withdrawal can be induced by life-history events

The above suggest that social withdrawal is part of an adaptive response which in itself can have beneficial properties. However, in the above situations the exposure to the cause and expression of social withdrawal was always of a temporary nature. An adaptive behavioral response to an acute situation can become a serious risk factor for an individual's health and quality of life if it becomes chronic, excessive and/or leading to lasting social isolation.

11.1. Adverse life events during critical periods

Early-life adverse experiences can lead to a change in the behavioral phenotype later in life including social behavior. These experiences may occur even as early as during gestation. As stated above, when a rodents' immune system is activated, they (transiently) display sickness behavior. The same can be observed in pregnant dams (see for example Kirsten et al., 2010). Interestingly, acute infection of the mother during gestation also holds consequences for the offspring. The consequence, however, persist into adulthood. Offspring from dams that were infected during gestation show long-term changes in behaviors such as diminished locomotor activity and social interaction (see for review Boksa, 2010). After maternal immune activation (MIA) social withdrawal can be found in mice (Shi et al., 2003; Smith et al., 2007) and male rats (Kirsten et al., 2010). It has also been implicated to play a role in the etiology of human neuropsychiatric disorders (see for review Estes and McAllister, 2016).

Not only pathogens, but also (social) stressors in the early life of an

animal can lead to social withdrawal later in life. Adverse social events shortly after weaning lead to a reduction of social behavior later in life. In juvenile mice (24 days old), social defeat stress exposure for one, five or ten consecutive days leads to social avoidance. This effect can be seen both acutely, one day after exposure, and four weeks after exposure. In contrast, adult mice (70 days old) show no change in social behavior after just one day of SDS and only show long-term effects after 10 consecutive days of SDS exposure (Mouri et al., 2018). This suggests that animals are particularly vulnerable to social stressors in this juvenile period, leading to social deficits during adulthood. Similarly to SDS, social isolation can induce social withdrawal later in life (Hol et al., 1999; Lukkes et al., 2009). Key in this reduction of social behavior appears to be the reduced ability for social play (Hol et al., 1999). Social play occurs mainly in the period around and after weaning and appears to play a key developmental role (see for review Vanderschuren and Trezza, 2014). This suggests that adverse events during specific key developmental periods can induce social deficits later in life. Evidence for this has also been found in humans. Children of mothers that experienced either the Dutch hunger winter (1944–1945) or the Chinese famine (1959–1961) show an increased prevalence of neuropsychiatric disorders (Brown et al., 1995; Susser and Lin, 1992; Xu et al., 2009). Both of these historical events subjected these children to prenatal stress by substantially lowering the nutritional intake of the mother. Similarly, adverse experiences during childhood pose a risk factor for neuropsychiatric disorders (Choi et al., 2017; Rhee et al., 2019), including those connected to social withdrawal. Along those lines, a higher exposure to adverse childhood experiences relates to increased SZ symptomatology, particularly when these adverse events are related to abuse and neglect (Carbone et al., 2019). From this we can conclude that life history events in both humans and rodents can have long-lasting effects in terms of social behavior. These effects seem to have adaptive value, if the environmental factor that led to the behavioral change would still be relevant as originally hypothesized by Belsky et al. (1991) in their adaptive calibration theory of adaptive life history strategies (Belsky et al., 1991). This theory proposes that early life experiences serve an evolutionary function by signaling to the offspring the amount of harshness and/or availability and predictability of resource information vital to the allocation of future reproductive effort. In harsh and/or unpredictable environments, it makes more sense to be aware of possible environmental risks. Avoidantly attached individuals, for example, have a more accessible rapid fight-flight schema and are quicker to react to perceived threats (Ein-Dor et al., 2011a, 2011b), indicating the adaptive advantages of such an avoidant attachment style (Szepsenwol and Simpson, 2019). However, in many of the aforementioned cases there is a mismatch between the environment during early life and the later environment, causing the expression of social withdrawal to be maladaptive (Schmidt, 2011).

11.2. Genetic predispositions for stress susceptibility

Stress and/or infection alone often only lead to behavioral deficits in a susceptible subpopulation. This susceptibility can come from being exposed to these adverse events in a particularly vulnerable developmental period, but often also genetic vulnerabilities appear to play an important role in connecting stress during particular periods to social impairments during adulthood. For example, Coutellier et al. (2015) showed that mice deficient for the gene *Npas4* exhibit cognitive deficits during adulthood after being exposed to mild chronic stress during adolescence, in contrast to wild-type animals (Coutellier et al., 2015). The *Npas4* gene also seems to influence social behavior in adult males born from a mother that was subjected to chronic restraint stress during gestation. Adult males heterozygous for the *Npas4* gene show decreased social interaction and a social recognition deficit, when compared to control animals (Heslin and Coutellier, 2018). More evidence comes from Abazyan et al. (2010), by making use of a mouse model carrying a mutant version of the gene Disrupted-In-Schizophrenia-1 (*DISC1*). In this study, adult mutant mice showed social withdrawal and other depression-related behaviors after maternal immune activation (MIA). Again, these behavioral alterations where not found in either control animals receiving MIA or in animals from which the mother was not infected (Abazyan et al., 2010). However, interactions between genetics and adverse events are not limited to the prenatal phase. Bartolomucci et al. (2010) show that mice heterozygous for the *SERT* gene displayed social withdrawal after being exposed to chronic social stress during adulthood, whereas social withdrawal was not seen in wild type mice or non-stressed animals (Bartolomucci et al., 2010). In humans a role for the *SERT* gene in stress vulnerability has also been suggested. Carriers of the so-called short allele appear to be at higher risk for depression after stressful life events when compared to carriers of the long allele (Caspi et al., 2003). These results, however, have not been consistently replicated, though a majority of the findings still point towards the initial findings (see for review Avshalom et al., 2010; Uher and McGuffin, 2008). More genes appear to play a role in stress susceptibility. Social interaction time could be decreased following adult subthreshold social defeat stress (SSDS) in mice in which Cacna1c was knocked out in the NAc (Terrillion et al., 2017). The *Cacna1c* gene has been also implicated in multiple neuropsychiatric disorders, including SZ and MDD (Smoller et al., 2013). Similarly, reducing *Slc6a15*, a neutral amino acid transporter, expression in specifically the D2 medium spiny neurons of the NAc leads to increase susceptibility to SSDS (Chandra et al., 2017). Also the *Slc6a15* gene has been identified as a risk factor for MDD (Kohli et al., 2011). Interestingly, CSDS also leads to reduced expression of both the *Cacna1c* (Terrillion et al., 2017) and the *Slc6a15* gene (Chandra et al., 2017). Together this suggests that strong stressors can alter the expression of disorder related genes specifically in components of the SDMN, thereby increasing susceptibility for developing social withdrawal.

12. Genetic risk factors for maladaptive social withdrawal

Social withdrawal is most probably caused by a combination of genetic and environmental factors. Both family and twin studies have provided evidence for a heritable component of social anxiety/avoidance (Hudson and Rapee, 2000). Social functioning in general is a continuously distributed trait in the population (Reeb-Sutherland et al., 2012), while decreased social functioning represents a common early manifestation of multiple disorders such as Schizophrenia, major depression, and Alzheimer Disease. As part of the PRISM project (Kas et al., 2019), which is focusing on transdiagnostic studies of shared symptomatology, it was hypothesized that continuity exists in the genetic underpinnings of social functioning as a trait in the general population and as a clinical symptom. As part of the project, a genome-wide association study (GWAS) was performed using a score based on 4 social functioning self-report questions in the UK Biobank sample (N = 342,461). The trait was significantly heritable, and the GWAS yielded 604 genome-wide significant single nucleotide polymorphisms (SNPs) in 19 independent loci. Significant genetic correlations of social functioning were indicated with schizophrenia and Major depression, but not with Alzheimer Disease. The social functioning trait also showed moderate genetic correlation with loneliness and social anxiety. This study shows that there is a significant genetic component to variation in population levels of social functioning. Genome-wide gene-based analyses - taking into account all SNPs within a gene - performed on the results of the SNP-wise GWAS of social functioning revealed 33 significant genes, including DRD2 (Bralten et al., 2019). In another study on social isolation and social interaction using the UK biobank sample, GWAS data was integrated with gene expression and epigenetic data to identify the relevant cell/tissue types implicated in the regulation of loneliness. Interestingly, this study observed enrichment of association signals in regions surrounding genes that are preferentially expressed in several brain tissues, such as the cerebellum, basal ganglia, and cortex (Day et al., 2018). This way, building relationships between 'social'

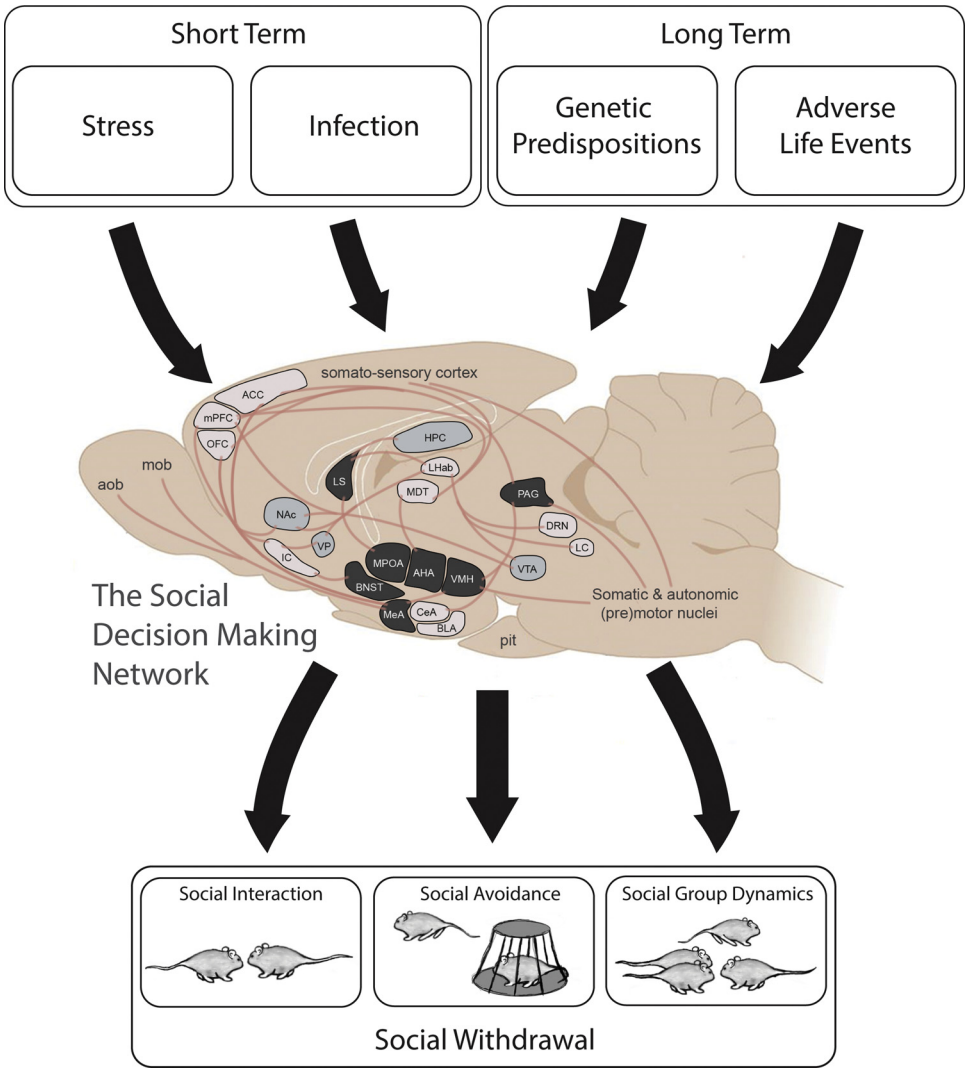

Fig. 1. Schematic map of the cortical and subcortical brain structures that characterizes the social decision-making network and the factors modulating this neural network leading to social withdrawal in animal models. Brain areas shaded in dark represent Newman's basic Social Behavior Network (SBN). Brain areas shaded lightly represent the additional mesolimbic reward structures that together with the SBN comprise O'Connell & Hofmann's SDMN. The brain areas in white are mainly the core cortical components of Brothers' and Dunbar's Cognitive Social Brain, as well as the main monoaminergic brainstem nuclei that importantly orchestrates the functional state of the entire SDMN. Stress and infection in a healthy individual can lead to temporary changes in the SDMN, inducing the display of social withdrawal. However, when these factors (adverse life events) occur at crucial development periods these effects can be long lasting. Genetic predisposition can alter the SDMN inducing either a direct effect on social behavior or lead to increased susceptibility to stressors. Social withdrawal, the ultimate outcome of these factors, can be displayed as lowered social interaction time, increased social avoidance and other alterations in the social group dynamics. ACC: anterior cingulate cortex; AHA: anterior hypothalamic area ; aob: Accessory olfactory bulb; BLA; basal lateral amygdala; BNST: bed nucleus stria terminalis; CeA: central amygdala; DRN: Dorsal raphe nucleus; HPC: Hippocampus; IC: insular cortex; LC: locus curoeleus; LHab: lateral habenula; LS: Lateral Septum; MDT: medial dorsal thalamus; mPFC: medial prefrontal cortex; MPOA: medial preoptic area; mob: medial olfactory bulb; NAc: Nucleus Accumbens; OFC; orbitofrontal cortex PAG: Periaqueductal grey area; pit: pituitary; VP: Ventral pallidum.

genes and neural networks associated to social functioning can be initiated. These findings, however, will require subsequent functional validation studies, such as those performed in rodent studies, to further our understanding on the functional relationship between genes, neural circuits and social functioning.

13. Concluding remarks

Social withdrawal is a common symptom of multiple neuropsychiatric disorders, often occurring prodromal to the disorder. Abundant evidence supports the view that this behavioral symptom emerges from a malfunctioning of the brain's so-called SDMN. Neuropsychiatric disordered patients that express excessive social withdrawal symptoms all show malfunctions in at least one component of the SDMN. Interestingly, the neuroanatomical architecture and molecular genetic characteristics of the SDMN are highly conserved across animals species, as is the expression of social withdrawal itself, suggesting that this behavior can be better understood when placed in an evolutionary framework. Manipulating SDMN components in model organisms (e.g., mice) can lead to profound alterations in social withdrawal. However, this behavior is also induced after exposure to a variety of ecological relevant environmental conditions. For example, social stressors and/or infectious agents can temporarily affect components of the SDMN during adulthood (Colyn et al., 2019; Wang and Quinn, 2010), leading to an adaptive social withdrawal response principally aimed at avoiding the adverse situation. Similar environmental factors encountered at crucial developmental time-points (e.g. during gestation or childhood) can lead to long-term alterations in components of the SDMN, inducing long-lasting social withdrawal (Lukkes et al., 2009; Mouri et al., 2018). In these situations, the displayed behavior is often no longer adaptive, as the environment that was responsible for inducing the behavioral adaptation may not be relevant anymore. The resulting social withdrawal might have been appropriate to prepare for a future harsh environment that never came into existence. Long-term alterations in the structural and/or functional properties of the SDMN can also find its root cause in genetic predispositions, which either directly lead to social withdrawal (Lee et al., 2018) or increase susceptibility to an environmental factor such as social stress (Chandra et al., 2017). These genetic predispositions are often related to neuropsychiatric disorders (see for example Kohli et al., 2011). Fig. 1 summarizes the heterogeneous etiology of social withdrawal. When social withdrawal becomes excessive and/or chronic, it can have serious negative health consequences that may even outweigh the potential adverse health consequences of the risk factors themselves (Holt-Lunstad et al., 2010).

Future research should take the heterogeneous origin of social withdrawal into account and make use of its evolutionary well-conserved neural and genetic basis. Clinical studies should benefit from the use of objective measures that translate better to the current model organisms employed to gain in-depth mechanistic knowledge of this pervasive and often disabling behavioral expression.

Acknowledgements

The PRISM project (www.prism-project.eu) has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115916. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA. This publication reflects only the authors' views neither IMI JU nor EFPIA nor the European Commission are liable for any use that may be made of the information contained therein.

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